# METFORMIN MODULATION EFFECTS ON INSULIN RESISTANCE-ASSOCIATED CELLULAR CHANGES IN HUMAN TENOCYTES

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## INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is reported to predispose to tendinopathy. There is no study yet investigating the direct effect of insulin resistance (IR) on tenocytes. Metformin (Met), an anti-diabetic drug, is reported to reverse cellular abnormalities by targeting several pathways. The aims of this study: **(1)** to determine the IR effects on human tenocytes (hTeno) glucose uptake and total collagen expression. **(2)** to determine the Met modulation effects on IR-induced cellular changes in hTeno.

## METHODS:

Hamstring tendons collected from subjects undergoing ACL reconstruction (N=6) for immunofluorescence staining on insulin receptor β-subunit (INSR-β), GLUT1 and GLUT4. Cells were divided into: (G1) Control: without any treatment; (G2) IR model: hTeno treated with 140 pg/ mL tumour necrosis factor-alpha and (G3) IR model + 0.1 mM Met. At 24 hours, the cells were harvested for glucose uptake (GU) assay. Cell culture supernatants were collected for total collagen assay (TCA).

## RESULTS:

Immunofluorescence staining showed the distribution of INSR-β, GLUT1 and GLUT4 were throughout the cell membrane (Figure 1). GU assay showed significant reduced in fold change of insulin-mediated GU in G2 (0.894 ± 0.077) compared to G1 (1.106 ± 0.066). With Met supplement, G3 (0.975 ± 0.052) showed a significant increase in GU. In TCA, the results showed G3 produced significantly higher in fold change of insulin-mediated total collagen (2.978 ± 0.112) compared to G1 (1.928 ± 0.433) and G2 (0.699 ± 0.146).

## DISCUSSIONS:

The finding of this study is consistent with the previous study on T2DM murine model, which reported that tendon is one of the insulin targeted tissues.[1] In addition, it had been reported that Met promoted GLUT4 translocation in 3T3-L1 pre-adipocyte cells[2], as well as stimulated the COL-I synthesis in rat bone marrow progenitor cells.[3]

## CONCLUSION:

IR reduced hTeno glucose uptake and total collagen expression. Metformin has a modulation effects on IR-induced hTeno. Future studies shall involve the analysis of IR-associated downstream pathways in hTeno which can potentially be used as future therapeutic approach for diabetic tendinopathy.

## REFERENCES:

1. Bawany et. al. ORS Annual Meeting 2015.
2. Lin YC et. al. Oncotarget 2017.
3. Korntner S et. al. Nature. 2017.

**Figure 1: Immunofluorescence Images**